

AD \_\_\_\_\_  
(Leave blank)

**Award Number:** W81XWH-12-1-0578

**TITLE:** Targeting Autophagy for the Treatment of TSC and LAM

**PRINCIPAL INVESTIGATOR:** Elizabeth Henske

**CONTRACTING ORGANIZATION:**

Brigham and Women's Hospital  
Boston, MA 02115-0110

**REPORT DATE:** October 2013

**TYPE OF REPORT:** Annual Report

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland 21702-5012

**DISTRIBUTION STATEMENT:** (Check one)

☒ X Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b>					
1. REPORT DATE (DD-MM-YYYY) October 2013		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 30September2012-29September2013	
4. TITLE AND SUBTITLE Targeting Autophagy for the Treatment of TSC and LAM				5a. CONTRACT NUMBER W81XWH-12-1-0578	
				5b. GRANT NUMBER W81XWH-12-1-0578	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Elizabeth Henske  E-Mail: EHENSKE@PARTNERS.ORG				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  Brigham and Women's Hospital One Blackfan Circle, Karp Bldg, 6 <sup>th</sup> Fl, Boston, MA 02115-5713				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT  Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT : Lymphangiomyomatosis (LAM), a disease that primarily affects women, is characterized by cystic lung destruction. LAM results from the proliferation of LAM cells that harbor mutations in the <i>TSC1</i> or <i>TSC2</i> genes, leading to activation of the mammalian target of rapamycin complex 1 (mTORC1). Recently, sirolimus (rapamycin) has been shown to stabilize lung function decline and decrease angiomyolipoma tumor size. Discontinuation of therapy results in progression of lung function decline and tumor growth, suggesting that continuous use is required to maintain its beneficial effects. Autophagy (self eating) is a mechanism by which tumor cells recycle proteins and organelles. Blocking TORC1, a known autophagy inhibitor, with rapamycin increases autophagy and promotes survival of TSC2-deficient cells. The Sirolimus and Autophagy Inhibition in LAM (SAIL) trial is a phase I clinical trial to test the safety and tolerability of a combination of hydroxychloroquine and sirolimus in women with LAM.  We will measure the effect of therapy using the following secondary endpoints: 1. Forced expiratory volume in 1 sec (FEV1), 2. Forced vital capacity (FVC), 3. 6-minute walk test (6MWT), 4. Angiomyolipoma size, 5. Quality of life and 6. VEGF-D serum levels					
15. SUBJECT TERMS sirolimus, hydroxychloroquine, lymphangiomyoleiomatosis					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	5	19b. TELEPHONE NUMBER (include area code)

## Table of Contents

	<u>Page</u>
Introduction.....	4
BODY.....	4
Key Research Accomplishments.....	4
Reportable Outcomes.....	4-5
Conclusion.....	5
References.....	5
Appendices.....	5

**INTRODUCTION:**

This is a phase I, open label, dose escalating, two-center trial of the combination of sirolimus and hydroxychloroquine in women with LAM. The combination of sirolimus (2mg adjusted to keep trough levels between 5-15ng/ml) and hydroxychloroquine (200mg or 400mg) will be taken orally daily for 6 months. Up to 18 female subjects ages 18 and older with LAM will be enrolled at Brigham and Women's Hospital in Boston, MA and the National Heart, Lung, and Blood Institute in Bethesda, MD. The primary endpoint of this study is safety and tolerability of the combination of sirolimus and hydroxychloroquine in LAM patients. This trial will also investigate whether, in LAM patients, 6 month of combination therapy results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy. The role of LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy will also be investigated. The projected duration of the trial is 4 years.

**KEY WORDS:**

sirolimus, hydroxychloroquine, lymphangioleiomyomatosis

**OVERALL PROJECT SUMMARY:**

This study is planning to enroll up to a total of 18 subjects at Brigham and Women's Hospital (BWH) and the National Heart, Lung, and Blood Institute (NHLBI). BWH obtained IRB approval on 6/21/2013 and is activated and enrolling subjects. The NHLBI received IRB approval on 9/20/2013 and has completed the site initiation visit. Four subjects were screened at BWH. Three women have been enrolled. One subject is still in screening. All three subjects have completed at least an 8 week course of hydroxychloroquine and sirolimus. Two subjects have completed a 24 week course of study drug. No serious adverse events have been reported.

There have been 4 amendments to the protocol.

**Summary of Amendment 01**

- The Department of Defense was added to the consent form. A prescreening script and prescreening questionnaire was added to the protocol to help identify eligible subjects for screening.

**Summary of Amendment 02**

- A study drug information sheet was created to distribute to enrolled subjects as requested by the DSMB during the meeting on 11/5/2012.
- The DSMB Charter was amended to include an additional DSMB meeting to review analysis data if data is collected before the 6 month timepoint.

**Summary of Amendment 03**

- Instructions for use of contraceptives were clarified in the protocol and consent form.

- **Summary of Amendment 04**

- A spirometry measurement was added to visit 6
- Urinalysis was included in visit 6
- Urine pregnancy was moved from visit 7 to visit 6
- Dose limiting toxicity for visual disturbances was further defined to include "Any visual disturbance as outlined in the risk section of this protocol or in the hydroxychloroquine package insert."
- Risk of stopping study drugs was added to the risk section of the protocol

Two DSMB meetings have been held on 11/5/2012 and 6/13/2013. Per protocol, the DSMB convened for an interim analysis of safety data on 8/6/2013. Safety data was reviewed and the DSMB approved the dose escalation. A second interim analysis will occur once 3 more patients have completed an 8 week course of therapy with sirolimus and hydroxychloroquine at 400mg/day.

The plan from the originally approved SOW will remain the same in the upcoming year.

**Subject Status**

Subject ID	Screening Date	Start of Study Drug	Last visit Completed	Status
01-001	11/19/2012	12/09/2012	Visit on 08/19/2013	Completed Study drug
01-002	03/22/2013	04/05/2013	Visit 5 on 09/25/2013	Completed Study drug
01-003	05/17/2013	05/28/2013	Visit 4 on 09/12/2013	On study drug
01-004	10/01/2013			

**KEY RESEARCH ACCOMPLISHMENTS:** Nothing to report

**CONCLUSION:** Nothing to report

**PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:** Nothing to report

**INVENTIONS, PATENTS, AND LICENSES:** Nothing to report

**REPORTABLE OUTCOMES:** Nothing to report

**OTHER ACHIEVEMENTS:** Nothing to report